CLAIMS

We claim:

1. A method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject in need of treatment, a vector comprising a promoter sequence in operable linkage with a polynucleotide sequence encoding an angiostatic gene product, wherein the angiostatic gene product is expressed in the target cells, thereby treating ocular neovascularization in the subject.

2. The method of claim 1, wherein the promoter sequence is a physiologically regulated promoter sequence or a constitutive promoter sequence.

3. The method of claim 2, wherein the physiologically regulated promoter sequence is a hypoxically responsive promoter sequence.

4. The method of claim 3, wherein the hypoxically responsive promoter sequence is a hypoxic response element (HRE).

5. The method of claim 2, wherein the constitutive promoter sequence is a CMV promoter.

6. The method of claim 1, wherein the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject.

7. The method of claim 1, wherein the ocular neovascularization is choroidal neovascularization or retinal neovascularization.

8. The method of claim 1, wherein the vector is a viral vector.

9. The method of claim 8, wherein the viral vector is a retroviral vector or an adeno-associated viral vector.

10. The method of claim 9, wherein the retroviral vector is a lentiviral vector.

11. The method of claim 10, wherein the lentiviral vector is an EIAV-based lentiviral vector.

12. The method of claim 1, wherein the target cells are retinal cells.

13. The method of claim 12, wherein the retinal cells are retinal pigment epithelial cells.

14. The method of claim 1, wherein delivery of the vector is via direct sub-retinal injection.

15. The method of claim 1, wherein the angiostatic gene product is selected from the group consisting of endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and pigment epithelium-derived factor (PEDF).

16. The method of claim 1, wherein the vector further comprises a polynucleotide sequence encoding at least one additional angiostatic gene product.

17. The method of claim 16, wherein the at least one additional angiostatic gene product is selected from the group consisting of endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and pigment epithelium-derived factor (PEDF).

18. The method of claim 1, wherein the angiostatic gene product is endostatin, and wherein the vector further comprises a polynucleotide sequence encoding angiostatin.

19. A vector comprising a hypoxically regulated promoter sequence in operable linkage with a polynucleotide sequence encoding an angiostatic gene product.

20. The vector of claim 19, wherein the vector is a viral vector.

21. The viral vector of claim 20, wherein the viral vector is a retroviral vector or an adeno-associated viral vector.

22. The retroviral vector of claim 21, wherein the retroviral vector is a lentiviral vector.

23. The lentiviral vector of claim 22, wherein the lentiviral vector is an EIAV-based lentiviral vector.

24. The vector of claim 19, wherein the angiostatic gene product is selected from the group consisting of endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and pigment epithelium-derived factor (PEDF).

25. The vector of claim 19, wherein the vector further comprises a polynucleotide sequence encoding at least one additional angiostatic gene product.

26. The vector of claim 25, wherein the at least one additional angiostatic gene product is selected from the group consisting of endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and pigment epithelium-derived factor (PEDF).

27. The vector of claim 19, wherein the angiostatic gene product is endostatin, and wherein the vector further comprises a polynucleotide sequence encoding angiostatin.

28. An autoregulatory cassette comprising a polynucleotide comprising:

(i) a construct comprising at least three hypoxia response elements (HRE) operably linked to a promoter;

(ii) a nucleic acid sequence encoding HIF-1, endothelial PAS domain protein (EPAS), or both, operably linked to the construct; and

(iii) one or more nucleic acid sequence(s) of interest (NOI), operably linked to the construct.

29. The polynucleotide of claim 28, wherein the promoter is an SV40 promoter or an MLV promoter.

30. The polynucleotide of claim 28, wherein each of the HREs comprises at least one HIF-1 binding site and wherein each of the HIF-1 binding sites comprises the nucleotide sequence CGTG.

31. The polynucleotide of claim 28, wherein the HREs are direct repeats.

32. The polynucleotide of claim 30, wherein one or more of the HREs comprises a phosphoglycerate kinase (PGK) HRE.

33. The polynucleotide of claim 32, wherein the PGK HRE comprises the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

34. The polynucleotide of claim 30, wherein one or more of the HREs comprises erythropoietin (EPO) HRE, LDH HRE, glucose trpt HRE, vascular endothelial cell growth factor (VEGF) HRE, NOS HRE, aldolase HRE, enolase HRE, or heme oxygenase HRE.

35. The polynucleotide of claim 30, wherein one or more of the HREs comprises the nucleic acid sequence of SEQ ID NO:12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23.

36. The polynucleotide of claim 28, wherein at least one of the HREs is a mutant HRE having reduced HIF binding activity.

37. The polynucleotide of claim 28, comprising at least four HREs linked to the promoter, wherein at least two of the HREs are positioned upstream (5') of the promoter and at least two of the HREs are positioned downstream (3') of the promoter.

38. The polynucleotide of claim 37, comprising at least six HREs, wherein at least three HREs are positioned upstream (5') of the promoter and at least three HREs are positioned downstream (3') of the promoter.

39. The polynucleotide of claim 38, wherein at least three of the HREs are phosphoglycerate kinase (PGK) HREs, operably linked to an SV40 promoter or an MLV promoter.

40. A vector comprising the polynucleotide of claim 28.

41. The vector of claim 40, wherein the vector is a viral vector.

42. The viral vector of claim 41, wherein the viral vector further comprises:

(i) a nucleotide sequence encoding an inhibitory RNA molecule capable of affecting the cleavage, directly or indirectly, of VHL RNA;

(ii) one or more inhibitory RNA molecules that binds to and prevents VHL RNA processing, expression, or both; or

(iii) a nucleotide sequence encoding a polypeptide capable of inhibiting the binding of VHL to Elongin B, Elongin C, or both.

43. The viral vector of claim 42, wherein the nucleotide sequence (iii) encodes a non-functional derivative of wild-type VHL.

44. The viral vector of claim 41, wherein the viral vector is a retroviral vector.

45. The viral vector of claim 41, wherein the viral vector is an adenoviral vector.

46. The viral vector of claim 41, wherein the viral vector is a lentiviral vector.